European Patent Office

EP 0 793 958 A2

EUROPEAN PATENT APPLICATION

Date of publication of application: 9/10/1997 Bulletin 1997/37

IPC7: A61K 9/16

Application No.: 97103306.3

Application date: 2/28/1997

Designated contracting states:
AT BE CH DE FR GB IE IT LI LU NL

Priority: 3/6/1996 DE 19608750

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Process for Preparing a Composition Containing Fenofibrate

The subject of the invention is a process of producing fenofibrate preparations using fenofibrate, surface-active agents and polyvinylpyrrolidone as well as, optionally, 1 or more other adjuvants and

using a mixing and a granulating and a subsequent drying, that is by which in that at first fenofibrate particles are mixed with polyvinylpyrrolidone particles and cross-linked polyvinylpyrrolidone particles as well as, optionally, other adjuvant particles, and then the mixture obtained is granulated with an aqueous solution of 1 or more surface-active agents in a constituent amount of at least 1.5 wt% relative to the dry granulate to be produced, and the granulate is dried.

Said process is simpler than those known in the art und leads nevertheless to products with approximately equally good therapeutic action as those obtained according to the state of the art.

Specification

The invention relates to a process of producing fenofibrate preparations with which fenofibrate preparations can be readily obtained with approximately equally good bioavailability and, as a consequence, equally good action as those produced in accordance with the state of the art.

Fenofibrate with the chemical designation 2-(4'-[4"-(chloro)-benzoyl]phenoxy)-2-(methyl)-propionic acid isopropylester is a known lipid reducer.

EP patent 330 532 teaches a process of producing fenofibrate preparations in which

(i) The fenofibrate and a solid, surface-active agent are intimately mixed and subsequently subjected to a common treatment with a jet mill,

(ii) Lactose and starch are added to the mixture obtained,

(iii) The entirety is granulated in the presence of water and

(iv) Granulated until a granulate containing at the most 1% water is obtained,

(v) The granulate is calibrated and

(vi) Polyvinylpyrrolidone and magnesium stearate are added.

It is stated that in order to increase the bioavailability of the fenofibrate, the common grinding (co-micronization) of fenofibrate and surface active agent is essential (Page 2, lines 21 to 22).

Furthermore, DE patent 35 03 681 describes a swellable polymer that is insoluble in water and is charged with a biologically active substance or a substance that is converted into one in vivo, obtainable by producing and grinding a mixture of this substance with a swellable polymer that is insoluble in water in a weight ratio of the cited substance : polymer of 1 : 0.1 to 1 : 100, which polymer can be cross-linked polyvinylpyrrolidone or cross-linked sodium carboxymethylcellulose.

Moreover, drugs are known from DE patent 31 52 519 that have a delayed release for oral administration, containing an active-substance layer with binding agents and containing a water-permeable, porous jacketing whose neutral core consists of inert binding agents selected from the group of raw sugar and lactose, optionally starch, and in which the neutral core is jacketed with a first layer containing active substance containing fenofibrate and/or its derivatives in a mixture with a binding agent from the group of talcum, silicon dioxide or their mixtures as well as stearic acid, and the granules comprise a second, outer layer formed from a microporous jacket, among other things with polyvinylpyrrodidone.

Furthermore, EP-A1-256 933 describes a process for producing a medicament in granular form in which in one stage a neutral core is moistened with an external, moist, adhesive layer that can be, among other things, based on polyvinylpyrrolidone, and then in another stage fenofibrate microparticles are applied onto the moistened core, advantageously by spraying, and the entirety is dried.

US patent 4, 800, 079 and 4, 961, 890 and FR-A1-2 602 423 relate to approximately the same process.

FR-A1-2 617047 teaches a fenofibrate preparation containing fenofibrate and a surface-active agent as well as dimethylisosorbide and optionally a gelling agent and excipients in capsules.

Moreover, GB patent 931 147 teaches a process of producing a retarding preparation by melting polyvinylpyrrolidone, fatty acids and the like and an active substance, forming droplets from the melt, spraying and forming pellets.

Furthermore, US patent 4, 925, 672 describes a combination of verapamil and fenofibrate of which the fenofibrate part can also contain polyvinylpyrrolidone. Nothing is stated about the process.

Furthermore, preparation No. 58 029 (Normalip pro®) capsules are described in the "Rote Liste" [German – "Red List") 1996 containing micronized fenofibrate, cross-linked polyvinylpyrrolidone (crospovidone) and sodium dodecylsulfate. The process of manufacture is not indicated but

it is known in professional circles that the manufacture takes place in accordance with the process of EP patent 330 532 discussed above.

The invention is based on the problem of creating fenofibrate preparations using fenofibrate, surface-active agents and polyvinylpyrrolidone as well as, if necessary, other adjuvants and using a mixing and a granulation and subsequent drying, by means of which process fenofibrate preparations with approximately equally good therapeutic action as those obtained according to the state of the art can be obtained in a manner that is surprisingly simpler than in the state of the art.

The above was surprisingly achieved in accordance with the invention without a common grinding of fenofibrate and solid surface-active agents.

The invention has as subject matter a process for producing fenofibrate preparations using fenofibrate, surface-active agents and polyvinylpyrrolidone as well as, optionally, 1 or more other adjuvants and using a mixing and a granulating and a subsequent drying, that is characterized in that at first fenofibrate particles are mixed with polyvinylpyrrolidone particles and cross-linked polyvinylpyrrolidone particles as well as, optionally, other adjuvant particles, and then the mixture obtained is granulated with an aqueous solution of 1 or more surface-active agents in a constituent amount of at least 1.5 wt% relative to the dry granulate to be produced, and the granulate is dried.

~~Micronized matter is preferably used as fenofibrate [sic -- this appears to mean "The fenofibrate used is micronized"?]~~

Preferably fenofibrate is used under a micronized form.

Compared to the teaching of EP patent 330 532 that has to carry out a common grinding of fenofibrate and a solid surface-active agent for achieving optimal bioavailability, it is surprising that this can be achieved by the invention even without the above in that the separately ground fenofibrate is merely mixed with polyvinylpyrrolidone and cross-linked polyvinylpyrrolidone without grinding and this mixture is granulated with the surface-active agent placed in aqueous solution and that it is not the case that the granulation takes place only after the introduction of the surface-active agent.

The polyvinylpyrrolidone present with the fenofibrate makes possible the construction of a granulate structure during the spraying with the solution of the surface-active agent or agents. It can be assumed that this also brings about a hydrophilization of the fenofibrate, which results in a better resorption and therewith an increasing of the bioavailability. The minimum amount of the surface-active agent or agents is critical since no satisfactory therapeutic result could be achieved below 1.5 wt%. The engineering simplification of the process in accordance with the invention compared to EP patent 330 532 resides primarily in the fact that according to the invention all adjuvants can be mixed in one and the same stage with the fenofibrate whereas in the cited, known process the other adjuvants must obligatorily be mixed in in an additional, separate stage on account of the obligatorily prescribed, common grinding (co-micronization) of the

fenofibrate and of the solid, surface-active agent. Furthermore, in the process of the invention the micronization alone of the fenofibrate brings about a reduction of the micronization volume compared to the common micronization of fenofibrate and of solid, surface-active agent and therewith brings about a lesser consumption of energy.

The process in accordance with the invention also differs basically from DE patent 35 03 681 in that in contrast to the common grinding of active substance and adjuvants described in it such as cross-linked polyvinylpyrrolidone (Claim 1, page 2, lines 23 to 33 and page 3, lines 34 to 37) with the assertion that the reduction of the particle size of drugs is frequently not effective enough when they are separately ground (page 2, lines 7 to 10), as already stated, a separate grinding of fenofibrate takes place and the ground fenofibrate is mixed only physically with the adjuvants. Furthermore, in contrast to DE patent 35 03 681 with the use of only a polymer that is insoluble in water, in the process of the invention the using of water-soluble polyvinylpyrrolidone for mixing with fenofibrate is indispensable for solving the problem posed. Also, in the process of the invention the granulating is performed with a surface-active agent that is not used at all in the cited publication.

Moreover, the product characteristics are also different in that in the process of DE patent 35 03 681 and EP patent 330 532 during the common grinding of active substance and adjuvants an amorphization of the active substance takes place whereas during the mere mixing in the process of the

invention the fenofibrate remains crystalline, as our own tests showed with a comparison of non-ground fenofibrate and only ground fenofibrate.

In contrast to DE patent 31 52 519 according to which the fenofibrate and the polyvinylpyrrolidone are present at different locations, namely, the first one in the first layer and the latter one in the external layer, and in which there is no mention of the two being mixed, in the process of the invention a mixing of the fenofibrate particles with polyvinylpyrrolidone particles and in addition with cross-linked polyvinylpyrrolidone particles takes place. The cited publication makes no mention of using cross-linked polyvinylpyrrolidone and a surface-active agent. According to its process cross-linked polyvinylpyrrolidone can not be used at all because, according to page 3, lines 5 to 51, the polymers are applied in solution.

In contrast to EP-A1-256 933, according to which an application such as the spraying on of fenofibrate onto the polyvinylpyrrolidone acting solely as binding agent is carried out, in the process of the invention a mixing of the fenofibrate with the polyvinylpyrrolidone and in addition with cross-linked polyvinylpyrrolidone takes place. There is also the difference from EP-A1-256 933, in which no cross-linked polyvinylpyrrolidone is used, which is even excluded according to its process, because a binding agent that is soluble in water must be used, that in the process of the invention cross-linked polyvinylpyrrolidone particles must be obligatorily also mixed in. A further difference resides in the fact that according to the process of the

invention, in contrast to that of the cited publication, the granulation is performed with a surface-active agent in another stage.

The process of the invention differs from that of FR-A1-2 617 047 basically in that in the first one the surface-active agent is added by granulation and only after the fenofibrate particles are mixed with the polyvinylpyrrolidone particles and cross-linked polyvinylpyrrolidone. There is the further difference that the two last-mentioned substances are entirely lacking in the cited publication.

The invention differs basically from US patent 4,925,672, in which no process is described, in that it concerns the inventing of a process, and in addition in that in contrast to the cited publication, in which there is no mention of a content of cross-linked polyvinylpyrrolidone and a surface-active agent, even these substances are used.

An anionic agent or agents are preferably used as surface-active means. It is preferable to use an alkalialkylsulfate or alkalialkylsulfates, especially sodium laurylsulfate, as **anionic** surface-active agent or agents.

It is also preferable to use a polyvinylpyrrolidone with a K value of 10 to 96, especially 25 to 35, as polyvinylpyrrolidone.

It is furthermore preferable to use a cross-linked polyvinylpyrrolidone with a specific surface (BET) of 0.1 to 1.5 m^2/g, especially 0.5 to 1.5 m^2/g and quite particularly 0.7 to 1.1 m^2/g as cross-linked polyvinylpyrrolidone.

A fenofibrate with particle sizes of 100% = or < 20μm is preferably used.

It is also preferable to use a polyvinylpyrrolidone with particle sizes of 100% = or < 500μm as polyvinylpyrrolidone.

It is furthermore preferable to use a cross-linked polyvinylpyrrolidone with particles sizes of 100% = or < 500μm as cross-linked polyvinylpyrrolidone.

The fenofibrate is preferably used in constituent amounts of 65 to 85wt%, especially 70 to 80wt% relative to the dry granulate.

It is furthermore preferable to use the surface-active agent or agents in constituent amounts of 1.5 to 7wt%, especially 2 to 5wt% relative to the dry granulate.

It is also preferable to use the surface-active agent or agents in a concentration of 1 to 5wt%, especially 2 to 3wt%.

It is furthermore preferred to use the polyvinylpyrrolidone in constituent amounts of 2 to 6wt%, especially 3 to 5wt% relative to the dry granulate.

It is also preferable to use the cross-linked polyvinylpyrrolidone in constituent amounts of 10 to 30wt%, especially 15 to 25wt% relative to the dry granulate.

The other adjuvant or adjuvants optionally used can be customary in the pharmaceutical art. Examples are starch, microcrystalline cellulose, lactose and magnesium stearate. The mixing in of this other adjuvant or adjuvants to the fenofibrate is advantageously carried out together with the polyvinylpyrrolidone and cross-linked polyvinylpyrrolidone; however, it

can also take place in a later or earlier phase, but in these instances the simplification of the process is less.

According to an embodiment of the process of the invention the granulate obtained is filled into capsules, in particular hard gelatin capsules.

The drying of the granulate, advantageously down to a residual moisture content of at the most 2.5wt%, especially at the most 2.0wt%, and its filling into capsules that optionally takes place can be carried out in a known manner.

The granulates or capsules produced in this manner and with their action that is equally as good as that of those produced in accordance with the state of the art can be used successfully therapeutically, especially as lipid reducers.

The invention will now be explained in detail using the following example.

Example

A mixture of 90 kg micronized fenofibrate with particle sizes of 100% = or < 15μm and 97 to 95% = or < 5μm, 4.5 kg polyvinylpyrrolidone particles DAB 10 with a K value of 27 to 32 and with particles sizes of 95% = or < 250μm and 10% < 50μm and 22.5 kg cross-linked polyvinylpyrrolidone particles DAB 10 with a specific surface (BET) of 0.9 m^2/g and with particle sizes of at least 98% = or < 250μm and at the most

60% = or < 50μm is pressed through a 0.8 mm sieve and mixed 10 minutes. A solution of ~~2.274~~ **2.475** kg sodium laurylsulfate NF 18 and 101.25 kg purified water was prepared separately. The first-cited powder mixture was then granulated with the last-cited solution in a fluid-bed granulator with an inlet temperature of approximately 20 to 40°C (outlet temperature 20± 5°C). The moist granulate **was dried in a drier at a temperature of 50± 5°C to a residual moisture of about 1.5± 5%. The dry granulate** was pressed through a 0.5 mm sieve. The mixture was subsequently mixed 10 minutes longer.

The granulate obtained in this manner was filled in a capsule filling machine into opaque HS hard gelatin capsules No. 1 with a Turkish blue cap and a white body. ~~405,000~~ **450,000** capsules with a capsule content of 265 mg each were filled with the granulate with a total weight of 119.475 kg.

The determination of the scientifically recognized therapeutic target sizes C_{max}, t_{max} AUC_t and AUC yielded no significant deviation between the present fenofibrate preparation produced in accordance with the invention and the one produced according to example 1 of EP patent 330 532.